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Iron Trichloride-Mediated Cascade Reaction of Aminosugar Derivatives for the Synthesis of Fused Tetrahydroisoquinoline−Tetrahydrofuran Systems

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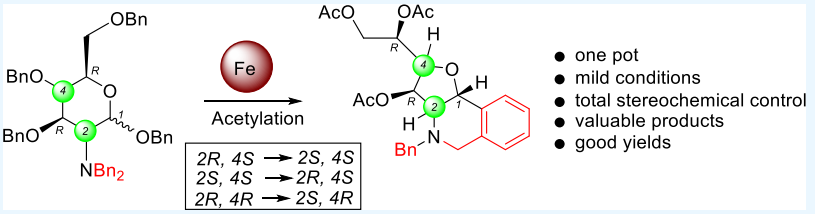

ABSTRACT: A method to obtain tetrahydroisoquinolines (THIQs) fused to tetrahydrofuran rings from aminosugar derivatives has been developed. The procedure relies on a key deprotection of benzyl ethers followed by a double-cyclization sequence, using $FeCl_3$ as the sole reagent. This tandem reaction affords the construction of novel fused polycyclic heterocycles with total stereochemical control.

INTRODUCTION

Tetrahydroisoquinolines (THIQs) are considered important "privileged scaffolds" that are part of many drugs and natural products.[1] The numerous THIQ-containing alkaloids created by nature exhibit antitumor, antiviral, antimalarial, and anti-inflammatory activities[2] and a wide number of THIQ derivatives have been developed as a novel class of therapeutic compounds with unique mechanisms of action.[3] The biological potential of THIQs analogues along their structure−activity relationship (SAR) has been recently updated.[4]

Therefore, to date, various methodologies are distinguished (Figure 1) according to the type of reaction that generates the heterocyclic ring, from the classical Pomeranz−Fritsch, Bischler−Napieralski, and Pictet−Spengler reactions (upper part of the figure) to intramolecular Lewis acid-catalyzed cyclization reactions [C_1−N_2],[5] double-cyclization [C_1−N_2/N_2−C_3],[6] and pericyclic reactions [C_1−N_2/C_4−C_{4a}][7] (lower part of the figure). The application of these strategies has allowed, for example, the synthesis of (*S*)-cryptostyline II[6] or (+)-homochelidonine.[7] An extensive compilation of stereochemical modifications of traditional methods developed from 2004 to 2015 has been reported.[8] Likewise, the versatility of Pictet−Spengler and related protocols in the construction of pharmacophores such as THIQs,[9] and an overview on synthetic routes versus enzymatic reaction has been published recently.[10] Furthermore, as optical enantiomers exert diverse biological activities, the asymmetric synthesis of THIQs has garnered a lot of attention in the scientific community. These strategies include the preparation of C-1-chiral THIQs by catalytic stereoselective processes[11] or by using imines in

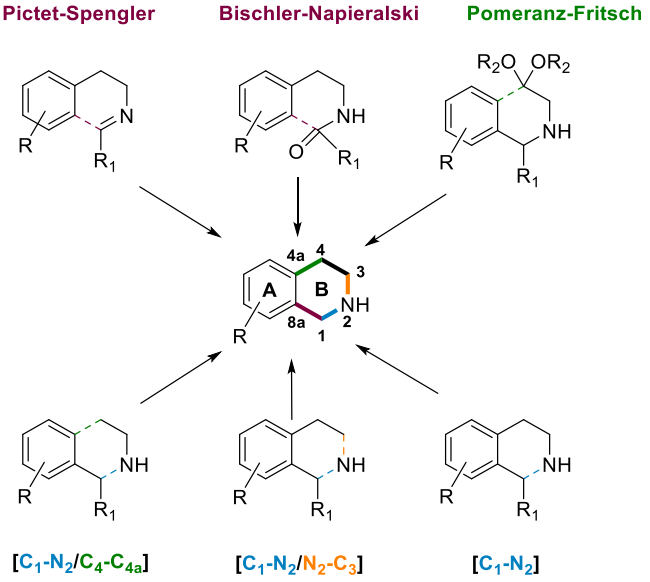

Figure 1. Representative strategies for the synthesis of THIQ skeleton.

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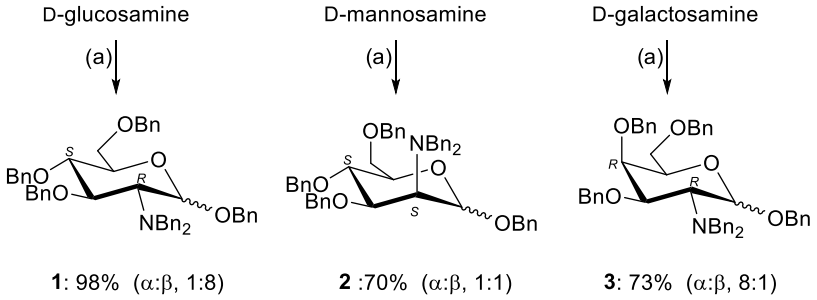
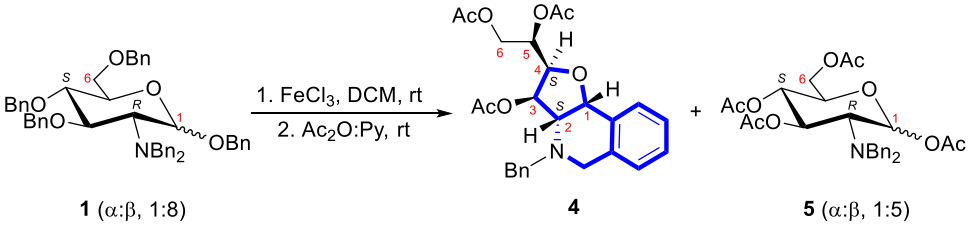
Scheme 1. Preparation of Starting Materials[a]



[a]Reaction conditions: see the general procedure for the synthesis of perbenzylated derivatives in the Experimental Section.

Scheme 2. Method to Obtain Compound 4 from D-Glucosamine[a]



[a]Reaction conditions and yields: see Table 1.

isoquinoline rings.[12] Moreover, simple approaches to access 3-substituted THIQ by iron-catalyzed tandem alcohol substitution and hydroamination using a sulfonamide nucleophile have been reported.[13]

While synthetic efforts have been devoted to the construction of 1-substituted, 1,3-disubstituted, 1,4-disubstituted, or 1,3,4-trisubstituted THIQs, the formation of more complex fused polycyclic systems containing THIQ has not been fully explored. A few examples are the construction of (spiro)polyheterocycles by combining an Ugi reaction with Pd catalyst[14] or 1,3-oxazolidines by cycloaddition of THIQs, aldehydes, and ethyl ketomalonate.[15]

The requirements to achieve the THIQ core are the existence of amines and aldehydes in the presence of strong acids. In turn, it is also necessary to incorporate an aromatic group to the structure to reach the alkaloid skeleton. In this work, we report an efficient $FeCl_3$-promoted cascade reaction of convenient functionalized aminosugars, as a tool that contains all of the requisites, to access THIQ-THF compounds under mild conditions.

RESULTS AND DISCUSSION

First, we prepared the benzylated derivatives of the following aminosugars: D-glucosamine, D-mannosamine, and D-galactosamine using an excess of NaH and benzyl bromide in DMF,[16] providing the perbenzylated compounds shown in Scheme 1.

Our initial investigation focused on examining the feasibility of cyclization of *N*-benzyl groups on anomeric carbon starting from compound **1** (Scheme 2). Its treatment with various commercially Lewis acids such as $AlCl_3$, $ZnCl_2$, or $BF_3{\cdot}OEt_2$ followed by acetylation gave a complex mixture of products (Table 1, entries 1−4). Fortunately, when the Lewis acid used was anhydrous $FeCl_3$, compound **4** was obtained in good to excellent yield, after acetylation. When the reaction time with anhydrous $FeCl_3$ was 30 min, the byproduct **5** was also formed in a 26% yield as a mixture of anomers.

Table 1. Optimization of the Reaction Conditions

entry	catalyst (equiv)	time (min)	yield (%)[a] 4
1	$AlCl_3$ (6)	120	[b]
2	$AlCl_3$ (6)	240	[b]
3	$ZnCl_2$ (6)	120	[b]
4	$BF_3{\cdot}OEt_2$ (12)	120	[b]
5	$FeCl_3$ (1.5)	120	[b]
6	$FeCl_3$ (3)	120	[b]
7	$FeCl_3$ (6)	120	52
8	$FeCl_3$ (12)	120	59
9	$FeCl_3$ (12)	240	45
10	$FeCl_3$ (12)	30	15
11	$FeCl_3$ (12)	45	97
12	$FeCl_3$ (12)	60	74
13	$SnCl_4$ (12)	45	[b]
14	$TiCl_4$ (12)	45	[b]

[a]Isolated yields. [b]Complex mixture, yields not determined.

To further optimize the reaction conditions, several experiments were realized. It was found that the reaction proceeded well in CH_2Cl_2 using 12 equiv of $FeCl_3$, acting as reagent (removal of the benzyl groups) and catalyst (cyclization reactions), with reaction times of 45 or 60 min at room temperature (entries 11−12). Complex mixtures were obtained when only 1.5 or 3 equiv of $FeCl_3$ were used (entries 5−6). When the reaction time was greater or less than 45 min (entries 7−10 and 12) or fewer equivalents of $FeCl_3$ were used (entry 7), the yields were lower. In all of the cases, the product was isolated after overnight acetylation with Ac_2O in Py. Attempts made with the mixture of anomers of compound **1** or with the anomers separately gave identical results, affording only product **4**.

It is known that $FeCl_3$ in CH_2Cl_2 at room temperature cleaves efficiently benzyl and methyl ethers, while acetate and benzoate groups are not affected.[17] Importantly, in this case, it

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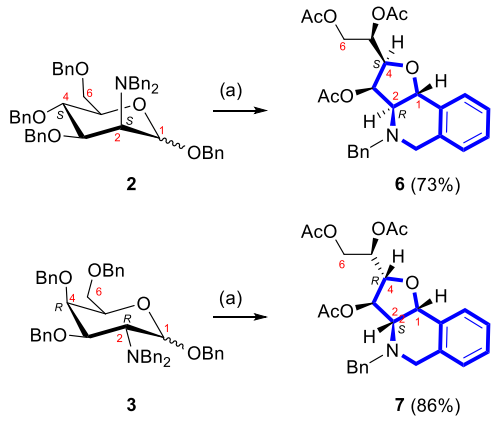
is the observation that only *O*-debenzylation occurred leaving the *N*-protection unaltered.

At this point, we considered that two Lewis acids ($SnCl_4$ and $TiCl_4$) that have been reported for the regioselective de-*O*-benzylation of poly-*O*-benzylated monosaccharides[18] could be successful in achieving the transformation under study. However, in both cases, compound **4** was not detected and a complex mixture of partially de-*O*-benzylated products was obtained (entries 13 and 14).

Under the optimized conditions (Table 1, entry 11), we explored the scope of this method with D-mannosamine and D-galactosamine. As illustrated in Scheme 3, the intramolecular

Scheme 3. Substrate Scope[a]



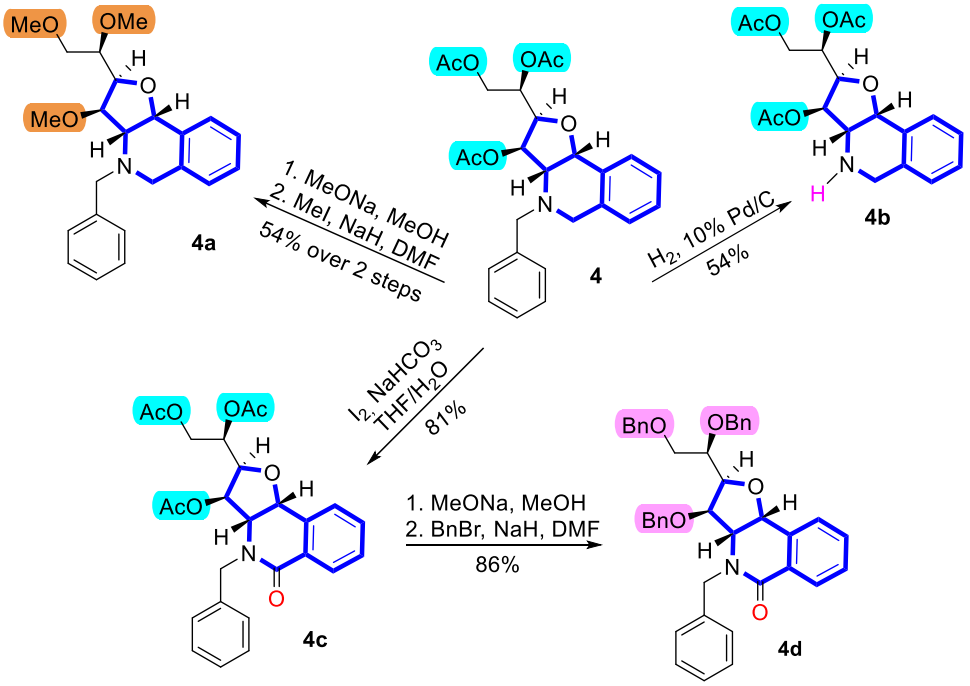
[a]Reaction conditions: perbenzylated compound (1 mmol), $FeCl_3$ (12 mmol) in CH_2Cl_2 (20 mL/mmol) was stirred at rt for 45 min; then, Ac_2O:Py (1:1) was added, and the mixture was stirred overnight at rt.

cyclization worked well allowing the formation of polyheterocycles **6** and **7**. This class of polyheterocycles containing a functionalized tetrahydrofuran unit fused to the THIQ nucleus is rarely found in the scientific literature. It is present in the bioactive Pars inhibitors[19] that also have potential ability for the treatment of inflammatory diseases; however, it is a planar structure without stereogenic centers. To date, a few methods have been published for the synthesis of such benzofuroisoquinolines and benzofuroisoquinolinones,[20] and more recently, structures of this type have been achieved by unprecedented sequential cycloadditions of quinazolinones with alkynes.[21]

Additionally, several transformations on substrate **4** were realized. First, a simple deacetylation of **4** followed by a methylation reaction gave compound **4a** (Scheme 4). The cleavage of the *N*-Bn bond with hydrogen using 10% Pd/C as catalyst[22] afforded compound **4b**, while its iodine-mediated oxidation[23] led to the corresponding lactam **4c**. Finally, **4c** was deacetylated and benzylated to give **4d** in good yields. Therefore, the stability of compound **4** allows straightforward conversions, which opens the possibility of accessing the construction of interesting and relatively complex structures.

It was observed that the preferential cyclization occurred through oxygen at C-4. Therefore, we decided to study the cyclization process by applying it to a compound with oxygen at C-4 protected. Preparation of compound **8** was achieved by controlled benzylation of glucosamine using 4:3.5 equiv of NaH:BnBr in DMF and subsequent acetylation.[16b,24] When compound **8** was treated directly with anhydrous $FeCl_3$, transesterification reactions occurred and a complex mixture of products was formed (Scheme 5), so it was necessary to get rid of the acetyl groups. Deacetylation of compound **8** followed by methylation led to compound **9**. Attempts to achieve the cyclization process from compound **9** using different equivalents of anhydrous $FeCl_3$ were performed (Table 2). If the reaction was conducted using less than 12 equiv of $FeCl_3$ the expected compound **10** was not detected (Table 2, entries 1−5). Only treatment of compound **9** with 12 equiv of $FeCl_3$ at rt led to ring closure from oxygen on C-5 (Table 2, entry 6). This reaction required a longer time of reaction than in the

Scheme 4. Preparation of Derivatives of Compound 4



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Scheme 5. Method to Obtain Compound 10 from D-Glucosamine

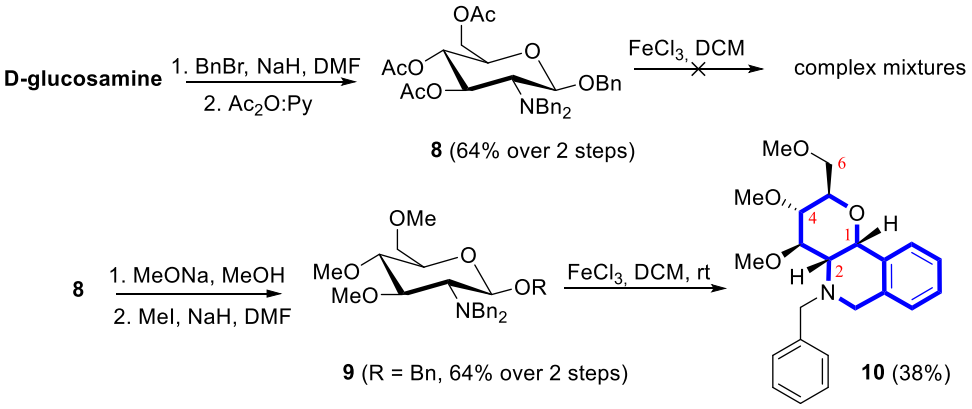

Table 2. Cyclization Conditions to Give Compound 10[a]

entry	$FeCl_3$ (equiv)	temperature (°C)	compound **10** (yield %)[b]
1	0.5	rt	nd
2	1	rt	nd
3	1.5	rt	nd
4	3	rt	nd
5	6	rt	nd
6	12	rt	**10** (38)[c,d]

[a]nd: not detected. [b]The reaction mixture was monitored via TLC at 45 min, 2 h, 3 h, 4 h, 7 h, and overnight. [c]Isolated yields. [d]The reaction was stirred overnight.

case of the furanose ring closure to form compound **4** and provided a poor yield of the final product **10** (38%) (Scheme 5). From this result, we conclude that the reaction cascade proceeds efficiently when the formation of the furanose ring is possible. When only cyclization to give a pyranose ring is possible, the reaction also occurs but with greater difficulty.

All compounds were characterized based on their one- (^{1}H and ^{13}C) and two-dimensional (COSY-G, HSQC) NMR spectra. For an easier discussion, the carbon atoms of the compounds are numbered as shown in Schemes 2 and 3 and Figure 2. Thus, the stereochemistry at C-1 of the prepared monosaccharides (**1**, **2**, **3**, and **9**) was established by analyzing the ^{1}H NMR $J_{1,2}$ value of each one. In the case of THIQ-THF compounds **4**, **7**, and THIQ-THP compound **10**, the *cis* disposition between H_1−H_2 is in agreement with the values of the coupling constant and the ROE effects. Additionally, in compound **7**, the *cis* arrangement for H_1−H_4 is observed. On the other hand, compound **6** obtained from the mannose derivative does not show a ROESY effect between H_1 and H_2 because it corresponds to a *trans* arrangement. In Figure 2, the mentioned T-ROESY correlations are shown by arrows.

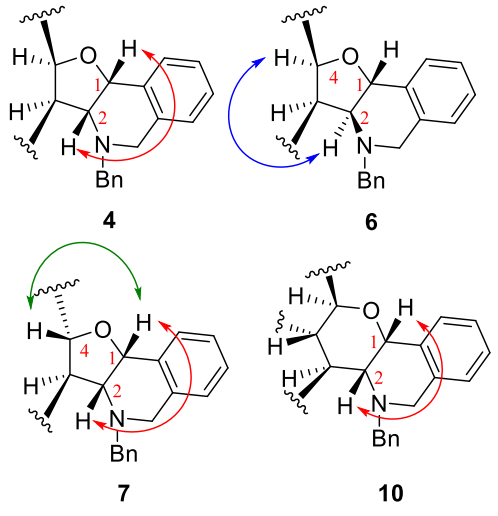

Figure 2. Observed ROESY interactions.

Based on our experimental results, a plausible mechanism of the reaction is proposed. Scheme 6 illustrates the mechanism for the case of compound **1**. The first step is the complete debenzylation of the substrate with the concomitant complexation of $FeCl_3$ to the ethereal oxygen atoms; subsequently, a rapid closure to the furanose form is produced by the attack of oxygen on C-4. At this point, the intermediate hemiacetal II equilibrates to the intermediate oxocarbenium ion III.

Regarding the acid-catalyzed cyclization reaction forming the bond between C_4 and C_{4a} (Figure 1), this method could be considered related to the Pomeranz−Fritsch and related reactions.[25] It is noteworthy that this strategy has been less explored than the traditional Pictet−Spengler or Bischler−Napieralski reactions and that only a few examples of its application have been described to date.[8]

The proposed mechanism would explain the results obtained (Table 1). Thus, when *O*-deprotection is not completed, complex mixtures of products were obtained. In the cases where complete debenzylation was achieved, there was insufficient time for cyclization to occur and the tetraacetylated compound **5** is obtained. Longer reaction times allow other closures leading to numerous reaction products.

ROESY spectra indicate that under acid reaction conditions, the aminosugar passes through the open-chain aldehyde isomer I (Scheme 6). The first cyclization promoted by the oxygen atom on C-4 gives hemiacetal II occurring with retention of its configuration (*S* for compounds **4** and **6** and *R* for compound **7**). Then, the hemiacetal loses a hydroxyl group giving a flat intermediate. A second cyclization by the less hindered face of the furan ring causes inversion of the configuration on C-2 in all cases (Figure 3).

CONCLUSIONS

In conclusion, an efficient synthetic method for the preparation of THIQ derivatives was developed through the iron-promoted domino selective debenzylation-intramolecular *O*-addition on aldehyde at C-1 and Pommeranz−Fritsch-type cyclization on a conveniently substituted aminosugar intermediate. This

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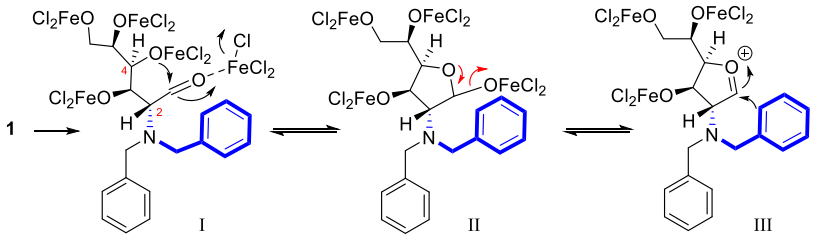
Scheme 6. Plausible Mechanism of the THIQ Formation Starting from D-Glucosamine



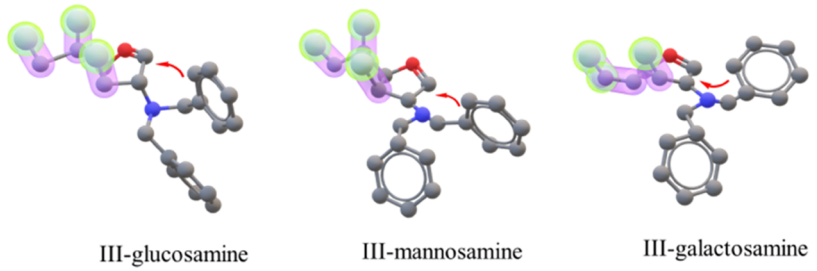


Figure 3. 3D representation of intermediates III corresponding to glucosamine, mannosamine, and galactosamine.

method provides a simple approach to access THIQ fused to highly substituted tetrahydrofuran or tetrahydropyran rings with full stereochemical control. Moreover, this procedure is fast, economical, and environmentally friendly. Further studies to extend the scope and synthetic utility of the described process are in progress in our laboratory.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded at 400, 500, and 600 MHz, and ^{13}C NMR at 100, 126, and 151 MHz, VTU 300.0 K. Chemical shifts are reported in parts per million. The residual solvent peak was used as an internal reference. For easier ^{1}H and ^{13}C assignations, the molecules are numbered according to semisystematic names, generally accepted for this class of compounds (see compounds **1** and **4**, Scheme 2). HRMS were analyzed by TOF MS ES^{+}. For analytical and preparative thin-layer chromatography, silica gel ready-foils and glass-backed plates (1 mm) were used, respectively, being developed with 254 nm UV light and/or spraying with Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O}, and heating at 150 °C. Column chromatography was performed using silica gel (0.015−0.04 mm) and *n*-hexane/EtOAc solvent systems. Circular layers of 1 mm of Merck silica gel 60 PF_{254} were used on a Chromatotron for centrifugal assisted chromatography. All reagents were obtained from commercial sources and used without further purification. Solvents were dried and distilled before use. All reactions were performed under a dry argon atmosphere.

General Procedure for the Synthesis of Compounds 1, 2, and 3. To a suspension of aminosugar (1.20 g, 4.6 mmol, 1 equiv) in anhydrous DMF (20 mL) was added NaH (1.6 g, 60% dispersion in mineral oil, 39.4 mmol, 8.5 equiv) at 0 °C, under an inert atmosphere. After stirring at room temperature for 30 min, benzyl bromide (5 mL, 41.4 mmol, 9 equiv) was added dropwise at 0 °C. The mixture was stirred at room temperature for 4 h. Then, NaH (0.1 g, 5 mmol, 1.1 equiv) was added, and after 30 min of stirring at room temperature, benzyl bromide (0.5 mL, 4.2 mmol, 0.9 equiv) was added at 0 °C. The reaction mixture was warmed at room temperature and stirred overnight. Then, MeOH was added to quench the excess of NaH. To the solution was added CH_2Cl_2 (30 mL), washed with water (15 mL), and added NH_4Cl saturated aqueous solution (15 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to give a yellow oil. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc, 5−10%) to give the final product.

(2S,3R,4R,5S,6R) and (2R,3R,4R,5S,6R)-N,N-Dibenzyl-2,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-3-amine ***1***. The compound was obtained as a mixture of anomers (α/β = 1:8) as a pale yellow viscous oil in 98% yield. Separation of the anomers was carried out by Chromatotron chromatography (*n*-hexane/EtOAc, 10%). Data for **1*α*** (minor): R_f = 0.33 (10% *n*-hexane/EtOAc). $[\alpha]_D^{20}$: +31.6 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.01 (1H, dd, J = 2.9, 9.1 Hz, H-2), 3.57 (1H, dd, J = 1.6, 8.8 Hz, H-6a), 3.66 (1H, dd, J = 7.2, 8.2 Hz, H-4), 3.71 (1H, dd, J = 3.2, 8.8 Hz, H-6b), 3.80−3.82 (1H, m, H-5), 3.84 (2H, d, J = 11.5 Hz, PhCH_2N−), 4.08 (2H, d, J = 11.5 Hz, PhCH_2N−), 4.24 (1H, dd, J = 7.1, 9.0 Hz, H-3), 4.48, 4.61 (2H, d, J = 10.1 Hz, PhCH_2O−), 4.49, 4.72 (2H, d, J = 8.9 Hz, PhCH_2O−), 4.55, 4.68 (2H, d, J = 9.5 Hz, PhCH_2O−), 4.92 (1H, d, J = 2.9 Hz, H-1), 4.94, 5.03 (2H, d, J = 9.5 Hz, PhCH_2O−), 7.08−7.44 (30H, m, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.0 (2C, PhCH_2N−), 60.6 (1C, C-2), 68.6 (1C, C-6), 69.8 (1C, PhCH_2O−), 70.3 (1C, C-5), 73.5 (1C, PhCH_2O−), 73.6 (1C, PhCH_2O−), 74.7 (1C, PhCH_2O−), 80.1 (1C, C-3), 80.6 (1C, C-4), 100.6 (1C, C-1), 126.6−128.5 (20C, Ar-C), 137.4, 137.8, 138.1, 139.2 (4C, Ar-quat), 140.8 (2C, Ar-quat). HRMS (ESI) calcd for $C_{48}H_{49}NO_5$: 719.3611; found: 719.3639. Anal. calcd for $C_{48}H_{49}NO_5$: C, 80.08; H, 6.86; N,1.95; found: C, 79.72; H, 6.90; N, 1.75. Data for **1*β*** (major): R_f = 0.27 (10% *n*-hexane/EtOAc). $[\alpha]_D^{20}$: −25.5 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.06 (1H, dd, J = 6.6, 8.2 Hz, H-2), 3.48 (1H, ddd, J = 1.8, 4.3, 8.2 Hz, H-5), 3.60 (1H, dd, J = 7.2, 8.1 Hz, H-4), 3.69 (1H, dd, J = 4.4, 8.9 Hz, H-6a), 3.74 (1H, dd, J = 1.8, 8.9 Hz, H-6b), 3.79 (dd, J = 7.2, 8.2 Hz, H-3), 3.81 (2H, d, J = 11.3 Hz, PhCH_2N−), 3.94 (2H, d, J = 11.5 Hz, PhCH_2N−), 4.50, 4.74 (2H, d, J = 9.0 Hz, PhCH_2O−), 4.58, 4.63 (2H, d, J = 10.1 Hz, PhCH_2O−), 4.63, 4.98 (2H, d, J = 9.7 Hz, PhCH_2O−), 4.67 (1H, d, J = 6.6 Hz, H-1), 4.86, 5.02

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(2H, d, J = 9.3 Hz, PhCH_2O−), 7.21−7.39 (30H, m, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 54.8 (2C, PhCH_2N−), 63.5 (1C, C-2), 69.3 (1C, C-6), 70.4 (1C, PhCH_2O−), 73.5 (1C, PhCH_2O−), 74.4 (1C, PhCH_2O−), 74.7 (1C, PhCH_2O−), 74.9 (1C, C-5), 79.3 (1C, C-4), 81.3 (1C, C-3), 100.6 (1C, C-1), 126.7−128.9 (20C, Ar-C), 137.6, 138.1, 138.1, 139.0 (4C, Ar-quat), 137.8 (2C, Ar-quat). HRMS (ESI) calcd for $C_{48}H_{49}NO_5$: 719.3611; found: 719.3630. Anal. calcd for $C_{48}H_{49}NO_5$: C, 80.08; H, 6.86; N, 1.95; found: C, 80.25; H, 6.87; N, 1.83.

(2S,3S,4R,5S,6R) and (2R,3S,4R,5S,6R)-N,N-Dibenzyl-2,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-3-amine ***2***. The compound was obtained as a mixture of anomers (α/β = 1:1) as a pale yellow viscous oil in 70% yield. Separation of the anomers was carried out by Chromatotron chromatography (n-hexane/EtOAc, 10%). Data for ***2α*** (minor): R_f = 0.36 (10% n-hexane/EtOAc). $[\alpha]_D^{20}$: +30.0 (c 0.04, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.18 (1H, dd, J = 4.7, 4.7 Hz, H-2), 3.65 (1H, dd, J = 4.2, 10.9 Hz, H-6a), 3.86 (1H, dd, J = 1.7, 10.9 Hz, H-6b), 3.89 (2H, d, J = 14.5 Hz, PhCH_2N−), 4.01 (1H, ddd, J = 1.7, 4.2, 8.9 Hz, H-5), 4.12 (1H, dd, J = 4.4, 8.9 Hz, H-4), 4.24 (2H, d, J = 14.5 Hz, PhCH_2N−), 4.27, 4.68 (2H, d, J = 11.3 Hz, PhCH_2O−), 4.31 (1H, dd, J = 4.6, 4.6 Hz, H-3), 4.49, 4.57 (2H, d, J = 12.4 Hz, PhCH_2O−), 4.53, 4.79 (2H, d, J = 12.2 Hz, PhCH_2O−), 4.66, 4.76 (2H, d, J = 11.6 Hz, PhCH_2O−), 5.10 (1H, d, J = 4.7 Hz, H-1), 7.21−7.32 (30H, m, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.6 (2C, PhCH_2N−), 63.8 (1C, C-2), 69.2 (1C, PhCH_2O−), 69.3 (1C, C-6), 71.1 (1C, PhCH_2O−), 73.3 (1C, PhCH_2O−), 73.6 (1C, PhCH_2O−), 77.2 (1C, C-5), 77.5 (1C, C-3), 79.9 (1C, C-4), 101.5 (1C, C-1), 126.7−128.4 (30C, Ar-C), 138.5, 138.6, 138.7, 138.8 (4C, Ar-*quat*), 140.5 (2C, Ar-quat). HRMS (ESI) calcd for $C_{48}H_{49}NO_5$: 719.3611; found: 719.3632. Anal. calcd for $C_{48}H_{49}NO_5$: C, 80.08; H, 6.86; N,1.95; found: C, 80.16; H, 6.97; N, 1.57. Data for ***2β*** (major): R_f = 0.33 (10% n-hexane/EtOAc). $[\alpha]_D^{20}$: −36.9 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.53 (1H, dd, J = 2.5, 5.5 Hz, H-2), 3.58 (1H, m, H-5), 3.73 (1H, dd, J = 5.6, 8.5 Hz, H-3), 3.80 (1H, dd, J = 4.7, 10.4 Hz, H-6a), 3.88 (1H, dd, J = 3.1, 10.4 Hz, H-6b), 4.12 (1H, dd, J = 8.4, 8.4 Hz, H-4), 4.17, 4.24 (2H, d, J = 14.0 Hz, PhCH_2N−), 4.28, 4.46 (2H, d, J = 11.9 Hz, PhCH_2O−), 4.49, 4.58 (2H, d, J = 12.2 Hz, PhCH_2O−), 4.54, 4.86 (2H, d, J = 11.1 Hz, PhCH_2O−), 4.69, 5.13 (2H, d, J = 12.0 Hz, PhCH_2O−), 4.77 (1H, d, J = 2.5 Hz, H-1), 7.19−7.32 (30H, m, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.6 (1C, C-2), 56.8 (2C, PhCH_2N−), 69.5 (1C, C-6), 70.8 (1C, PhCH_2O−), 71.0 (1C, PhCH_2O−), 73.1 (1C, PhCH_2O−), 74.3 (1C, PhCH_2O−), 74.5 (1C, C-4), 75.4 (1C, C-5), 81.5 (1C, C-3), 102.3 (1C, C-1), 126.5−129.3 (30C, Ar-C), 138.0, 138.3, 138.3, 139.6 (4C, Ar-quat), 141.4 (2C, Ar-*quat*). HRMS (ESI) calcd for $C_{48}H_{49}NO_5$: 719.3611; found: 719.3639. Anal. calcd for $C_{48}H_{49}NO_5$: C, 80.08; H, 6.86; N, 1.95; found: C, 79.76; H, 6.84; N, 2.08.

(2S,3R,4R,5R,6R) and (2R,3R,4R,5R,6R)-N,N-Dibenzyl-2,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-3-amine ***3***. The compound was obtained as a mixture of anomers (α/β = 8:1) as a pale yellow viscous oil in 73% yield. Separation of the anomers was carried out by Chromatotron chromatography (n-hexane/EtOAc, 10%). Data for ***3α*** (major): R_f = 0.31 (10% n-hexane/EtOAc). $[\alpha]_D^{20}$: +45.1 (c 0.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.48 (1H, dd, J = 4.9, 8.2 Hz, H-2), 3.70 (3H, m, H-5, 2H-6), 3.94 (5H, m, H-4, 2PhCH_2N−), 4.33, 4.53 (2H, d, J = 11.3 Hz, PhCH_2O−), 4.43, 4.79 (2H, d, J = 12.0 Hz, PhCH_2O−), 4.47 (3H, m, H-3, 2PhCH_2O−), 4.50, 4.72 (2H, d, J = 11.8 Hz, PhCH_2O−), 4.97 (1H, d, J = 4.8 Hz, H-1), 7.18−7.30 (30H, m, Ar-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 55.8 (2C, PhCH_2N−), 66.7 (1C, C-2), 69.5 (1C, PhCH_2O−), 70.7 (1C, C-6), 71.9 (1C, PhCH_2O−), 72.9 (1C, PhCH_2O−), 73.4 (1C, PhCH_2O−), 77.9 (1C, C-3), 78.3 (1C, C-5), 81.5 (1C, C-4), 102.0 (1C, C-1), 126.8−128.5 (30C, Ar-C), 138.1, 138.2, 138.5, 138.6 (4C, Ar-*quat*), 140.3 (2C, Ar-quat). HRMS (ESI) calcd for $C_{48}H_{49}NO_5$: 719.3611; found: 719.3629. Anal. calcd for $C_{48}H_{49}NO_5$: C, 80.08; H, 6.86; N,1.95; found: C, 79.82; H, 6.96; N, 1.73. Data for ***3β*** (minor): R_f = 0.25 (10% n-hexane/EtOAc). $[\alpha]_D^{20}$: −17.3 (c 0.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.46−3.49 (2H, m, H-2, H6), 3.59−3.65 (3H, m, H-3, H-5, H-6), 3.81 (2H, d, J = 13.9, PhCH_2N−), 3.86 (2H, d, J = 13.8, PhCH_2N−), 4.02 (1H, d, J = 2.2 Hz, H-4), 4.45−4.52 (5H, m, H-1, 2PhCH_2O−), 4.57 (1H, d, J = 11.5 Hz, PhCH_2O−), 4.78 (2H, d, J = 11.4 Hz, PhCH_2O−), 4.91 (1H, d, J = 11.6 Hz, PhCH_2O−), 7.14−7.34 (30H, m, Ar-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 55.0 (2C, PhCH_2N−), 59.8 (1C, C-6), 69.0 (1C, C-3), 70.4 (1C, PhCH_2O−), 71.3 (1C, PhCH_2O−), 72.2 (1C, C-4), 73.3 (1C, C-2), 73.6 (1C, PhCH_2O−), 74.3 (1C, PhCH_2O−), 79.9 (1C, C-5), 101.3 (1C, C-1), 126.5−128.9 (30C, Ar-C), 137.8, 138.0, 138.3, 138.6 (4C, Ar-quat), 140.5 (2C, Ar-quat). HRMS (ESI) calcd for $C_{48}H_{49}NO_5$: 719.3611; found: 719.3602. Anal. calcd for $C_{48}H_{49}NO_5$: C, 80.08; H, 6.86; N,1.95; found: C, 79.86; H, 7.12; N, 1.83.

(2R,3S,4R,5R)-2-(Acetoxymethyl)-6-(benzyloxy)-5-(dibenzylamino)tetrahydro-2H-pyran-3,4-diyl diacetate ***8***. To a suspension of D-glucosamine (1.0 g, 4.6 mmol) in anhydrous DMF (15 mL) under an inert atmosphere was added NaH (0.7 g, 60% dispersion in mineral oil, 17.2 mmol) at 0 °C. After stirring at room temperature for 1 h, benzyl bromide (1.9 mL, 16.2 mmol) was added dropwise at 0 °C, and the mixture was stirred at room temperature overnight. Then, MeOH was added to quench the excess of NaH and DMF was removed under vacuum. The crude residue was dissolved in pyridine, followed by the addition of acetic anhydride and the reaction mixture was stirred overnight at room temperature. Then, the pyridine was removed and the crude was dissolved in CH_2Cl_2 (50 mL) and washed with 2 M HCl solution (3 × 25 mL), water (3 × 25 mL), and brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow oil. The residue was purified by flash column chromatography on silica gel (n-hexane/EtOAc, 15−20%) to give compound **8** as the major product (1.7 g, 3.0 mmol, 64%). Data for **8**: R_f = 0.44 (30% n-hexane/EtOAc). $[\alpha]_D^{20}$: −0.5 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.04 (3H, s, −COCH_3), 2.09 (3H, s, −COCH_3), 2.13 (3H, s, −COCH_3), 3.01 (1H, dd, J = 8.4, 10.5 Hz, H-2), 3.63 (1H, ddd, J = 2.4, 5.1, 10.4 Hz, H-5), 3.67 (2H, d, J = 12.9 Hz, PhCH_2N−), 3.84 (2H, d, J = 12.9 Hz, PhCH_2N−), 4.16 (1H, dd, J = 2.4, 12.2 Hz, H-6a), 4.30 (1H, dd, J = 12.2, 5.1 Hz, H-6b), 4.71, 5.04 (2H, d, J = 11.6 Hz, PhCH_2O−), 4.76 (1H, d, J = 8.4 Hz, H-1), 4.93 (1H, dd, J = 9.0, 10.0 Hz, H-4), 5.36 (1H, dd, J = 9.0, 10.5 Hz, H-3) 7.24−7.51 (15H, m, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.5 (1C, −COCH_3), 20.6 (1C, −COCH_3), 20.8 (1C, −COCH_3), 54.1 (2C, PhCH_2N−), 61.2 (1C, C-2), 62.3 (1C, C-6), 70.0 (1C, C-4), 70.6 (1C, PhCH_2O−), 70.7 (1C, C-3), 71.4 (1C, C-5), 100.5 (1C, C-1), 126.9−129.1 (15C, Ar-C), 136.7 (1C, Ar-quat), 139.1 (2C, Ar-quat), 169.5,

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170.3, 170.6 (3C, −$COCH_3$). HRMS (ESI) calcd for $C_{33}H_{38}NO_2$ $[M + H]^+$: 576.2597; found: 576.2595.

(2R,3R,4R,5S,6R)-N,N-Dibenzyl-2-(benzyloxy)-4,5-dimethoxy-6-(methoxymethyl)-tetrahydro-2H-pyran-3-amine ***9***. A mixture of compound **8** (0.96 g, 1.7 mmol) and sodium methoxide (271 mg, 5 mmol) in dry methanol (10 mL/mmol) was stirred overnight under an inert atmosphere. Then, the reaction mixture was diluted with methanol, filtered through Amberlite IR-120, and the solvent was removed under reduced pressure. To a suspension of the resulting crude in anhydrous DMF were added NaH (0.4 g 60% dispersion in mineral oil, 6 equiv, 10.0 mmol) and MeI (3.2 mL, 30 equiv, 50.2 mmol). After stirring the reaction mixture overnight, same quantities of NaH and MeI were added. The reaction was monitored via TLC. When completion was detected, the mixture was diluted with CH_2Cl_2, neutralized with a saturated aqueous solution of NH_4Cl, and washed with water. The aqueous fraction was reextracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, concentrated under vacuum, and purified by column chromatography on silica gel (*n*-hexane/EtOAc, 15%) to afford compound **9** (0.44 g, 0.9 mmol, 54%) as a colorless viscous oil. Data for **9**: R_f = 0.12 (10%, *n*-hexane/EtOAc). $[\alpha]_D^{20}$: −4.9 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.85 (1H, dd, J = 8.2, 10.1 Hz, H-2), 3.17 (1H, dd, J = 8.4, 9.8 Hz, H-4), 3.22 (1H, ddd, J = 1.9, 4.7, 9.9 Hz, H-5), 3.40 (4H, overlap H-3, CH_3O−), 3.50 (3H, s, CH_3O−), 3.54 (1H, dd, J = 4.7, 10.6 Hz, H-6a), 3.61 (4H, overlap H6b, CH_3O−), 3.77 (2H, d, J = 13.8 Hz, PhCH_2N−), 3.88 (2H, d, J = 13.8 Hz, PhCH_2N−), 4.51 (1H, d, J = 8.1 Hz, H-1), 4.54, 4.95 (2H, d, J = 11.7 Hz, PhCH_2O−), 7.17−7.48 (15H, m, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.1 (2C, PhCH_2N−), 59.3 (1C, −OCH_3), 59.5 (1C, −OCH_3), 60.2 (1C, −OCH_3), 63.0 (1C, C-2), 70.5 (1C, C-2), 71.6 (2C, PhCH_2O−), 74.6 (1C, C-5), 80.7 (1C, C-4), 82.8 (1C, C-3), 100.8 (1C, C-1), 126.7−128.9 (15C, Ar-C), 137.7 (1C, Ar-quat), 140.0 (2C, Ar-quat). HRMS (ESI) calcd for $C_{30}H_{37}NO_5$ $[M + Na]^+$: 514.2569; found: 514.2556.

General Procedure for the Synthesis of THIQ Derivatives. To a solution of perbenzylated aminosugar (100 mg, 0.14 mmol) in dry CH_2Cl_2 (3 mL), anhydrous iron trichloride (271 mg, 1.7 mmol) was added, under an inert atmosphere, and the reaction was stirred for 45 min at room temperature. When the reaction was completed, CH_2Cl_2 was removed under vacuum. Then, a mixture of Py:Ac_2O (1 mL, 1:1) was added to the flask and stirred overnight at room temperature. The reaction mixture was concentrated under vacuum in the presence of toluene. Then, brine was added (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with 10% HCl solution (5 mL) and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc, 20%) to give the final product.

(R)-1-((2S,3R,3aS,9bR)-3-Acetoxy-4-benzyl-2,3,3a,4,5,9b-hexahydrofuro[3,2c]isoquinolin-2-yl)ethane-1,2-diyldiacetate ***4***. The compound was obtained as an orange viscous oil, (63 mg, 0.14 mmol, 97%). Data for **4**: R_f = 0.22 (20%, *n*-hexa-ne/EtOAc). $[\alpha]_D^{20}$: +34.3 (c 0.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.98 (6H, s, 2x −$COCH_3$), 2.09 (3H, s, −$COCH_3$), 3.35 (1H, d, J = 5.8 Hz, H-2), 3.37, 3.78 (2H, d, J = 15.0 Hz, PhCH_2N−), 3.53, 4.27 (2H, d, J = 14.0 Hz, PhCH_2N−), 4.16 (1H, dd, J = 5.8, 12.2 Hz, H-6a), 4.20 (1H, dd, J = 3.8, 9.4 Hz, H-4), 4.53 (1H, dd, J = 2.3, 12.2 Hz, H-6b), 5.20 (1H, d, J = 5.8 Hz, H-1), 5.32 (ddd, J = 2.3, 5.8, 9.2 Hz, H-5), 5.72 (1H, d, J = 3.8 Hz, H-3), 6.98−7.34 (9H, m, Ar-H). ^{13}C-NMR (151 MHz, $CDCl_3$): δ 20.7 (1C, −$COCH_3$), 20.8 (1C, −$COCH_3$), 21.0 (1C, −$COCH_3$), 52.6 (1C, PhCH_2N−), 59.8 (1C, PhCH_2N−), 63.7 (1C, C-6), 68.3 (1C, C-5), 69.2 (1C, C-2), 74.1 (1C, C-3), 75.8 (1C, C-1), 76.1 (1C, C-4), 125.8−129.0 (9C, Ar-C), 132.1, 134.8, 137.9 (3C, Ar-quat), 169.8, 170.0, 170.7 (3C, −$COCH_3$). HRMS (ESI) calcd for $C_{26}H_{29}NO_7$: 467.1944; found: 467.1926. Anal. calcd for $C_{26}H_{29}NO_7$: C, 66.80; H, 6.25; N, 3.00; found: C, 66.78; H, 6.27; N, 2.65.

(2R,3R,4R,5S,6R) and (2S,3R,4R,5S,6R)-6-(Acetoxymethyl)-3-(dibenzylamino)tetrahydro-2H-pyran-2,4,5-triyl triacetate ***5***. Following the above procedure but leaving only 30 min of treatment of perbenzylated D-glucosamine with iron trichloride, **4** (15%) and **5**, a viscous oil (10 mg, 0.02, 26%), as a mixture of anomers (α/β, 1:5) were obtained as final products. Data for **5**: R_f = 0.13 (20%, *n*-hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.93 (s, −$COCH_3\alpha$), 1.96 (s, −$COCH_3\beta$), 1.97 (s, −$COCH_3\alpha$), 1.98 (s, −$COCH_3\alpha$), 1.99 (s, −$COCH_3\beta$), 2.05 (s, −$COCH_3\beta$), 2.12 (s, −$COCH_3\alpha$), 2.18 (s, −$COCH_3\beta$), 3.05 (dd, J = 8.9, 10.5 Hz, H-2β), 3.23 (dd, J = 3.7, 11.2 Hz, H-2α), 3.58 (m, PhCH_2N−), 3.66 (ddd, J = 2.1, 4.6, 10.2 Hz, H-5β), 3.74 (d, J = 13.1 Hz, PhCH_2N−), 3.93 (m, H-6β, H-6α, H-5α, 2x PhCH_2N−), 4.21 (dd, J = 4.8, 12.5 Hz, H-6β, H-6α), 4.87 (dd, J = 9.1, 10.1 Hz, H-4β), 4.92 (dd, J = 9.2, 10.1 Hz, H-4α), 5.41 (dd, J = 9.0, 10.4 Hz, H-3β), 5.69 (dd, J = 9.0, 11.2 Hz, H-3α), 5.78 (d, J = 8.8 Hz, H-1β), 6.07 (d, J = 3.7 Hz, H-1α), 7.17−7.27 (m, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.7 (2C, −$COCH_3$), 20.8 (1C, −$COCH_3$), 20.8 (1C, −$COCH_3$), 21.1 (1C, −$COCH_3$), 21.2 (1C, −$COCH_3$), 21.4 (1C, −$COCH_3$), 21.4 (1C, −$COCH_3$), 54.8 (1C, PhCH_2N−), 55.8 (1C, PhCH_2N−), 57.9 (1C, C-2α), 60.2 (1C, C-2β) 61.7 (1C, C-6β), 61.8 (1C, C-6α), 69.2 (1C, C-5α), 69.3 (1C, C-4β), 69.7 (1C, C-4α), 70.6 (1C, C-3α), 71.2 (1C, C-3β), 72.3 (1C, C-5β), 92.0 (1C, C-1β), 93.0 (1C, C-1α), 127.4−129.2 (10C, Ar-C), 138.6, 139.1 (2C, Ar-quat), 168.9−170.7 (4C, −$COCH_3$). HRMS (ESI) calcd for $C_{28}H_{33}NO_9$ $[M + H]^+$: 528.2234; found: 528.2238.

(R)-1-((2S,3R,3aR,9bS)-3-Acetoxy-4-benzyl-2,3,3a,4,5,9b-hexahydrofuro[3,2c]isoquinolin-2-yl)ethane-1,2-diyl diacetate ***6***. The compound was obtained as a colorless viscous oil (28 mg, 0.06 mmol, 73%). Data for **6**: R_f = 0.11 (20%, *n*-hexane/EtOAc). $[\alpha]_D^{20}$: −20.4 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.86 (3H, s, −$COCH_3$), 1.99 (3H, s, −$COCH_3$), 2.07 (3H, s, −$COCH_3$), 3.50, 3.80 (2H, d, J = 14.5 Hz, PhCH_2N−), 3.61, 3.82 (2H, d, J = 13.1 Hz, PhCH_2N−), 3.74 (1H, dd, J = 5.4, 8.5 Hz, H-2), 4.15 (1H, dd, J = 3.6, 9.1 Hz, H-4), 4.18 (1H, dd, J = 5.2, 12.3 Hz, H-6a), 4.56 (1H, dd, J = 2.4, 12.3 Hz, H-6b), 4.99 (1H, d, J = 8.5 Hz, H-1), 5.20 (1H, ddd, J = 2.4, 5.2, 9.1 Hz, H-5), 5.64 (1H, dd, J = 3.6, 5.4 Hz, H-3), 6.99 (1H, d, J = 7.4 Hz, Ar-H), 7.22−7.34 (7H, m, Ar-H), 7.43 (1H, d, J = 7.4 Hz, Ar-H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 20.8 (1C, −$COCH_3$), 20.8 (1C, −$COCH_3$), 21.0 (1C, −$COCH_3$), 50.5 (1C, PhCH_2N−), 59.8 (1C, PhCH_2N−), 63.3 (1C, C-6), 63.7 (1C, C-2), 68.5 (1C, C-5), 72.6 (1C, C-3), 74.7 (1C, C-1), 77.8 (1C, C-4), 126.0−138.1 (9C, Ar-C), 134.1, 135.2, 138.1 (3C, Ar-quat), 169.7, 170.2, 170.7 (3C, −$COCH_3$). HRMS (ESI) calcd for $C_{26}H_{29}NO_7$: 467.1944; found: 467.1955. Anal. calcd for $C_{26}H_{29}NO_7$: C, 66.80; H, 6.25; N, 3.00; found C, 66.85; H, 6.41; N, 3.15.

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*(R)-1-((2R,3R,3aS,9bR)-3-Acetoxy-4-benzyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]isoquinolin-2-yl)ethane-1,2-diyl diacetate **7**.* The compound was obtained as a colorless viscous oil (86%). Data for **7**: R_f = 0.33 (30%, *n*-hexane/EtOAc). $[\alpha]_D^{20}$: +29 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.88 (3H, s, $-COCH_3$), 2.00 (3H, s, $-COCH_3$), 2.11 (3H, s, $-COCH_3$), 3.43, 3.89 (2H, d, J = 15.3 Hz, PhCH_2N−), 3.50 (1H, dd, J = 4.2, 6.4 Hz, H-2), 3.51, 4.03 (2H, d, J = 13.8 Hz, PhCH_2N−), 4.10−4.14 (2H, m, H-4 and H-6a), 4.35 (1H, dd, J = 4.3, 11.9 Hz, H-6b), 5.05 (1H, d, J = 6.4 Hz, H-1), 5.21 (1H, ddd, J = 4.3, 4.3, 8.7 Hz, H-5), 5.55 (1H, dd, J = 4.2, 5.9 Hz, H-3), 6.98−7.27 (9H, m, Ar-H). ^{13}C-NMR (151 MHz, $CDCl_3$): δ 20.6 (1C, $-COCH_3$), 20.7 (1C, $-COCH_3$), 21.0 (1C, $-COCH_3$), 51.4 (1C, PhCH_2N−), 59.1 (1C, PhCH_2N−), 62.8 (1C, C-6), 67.8 (1C, C-2), 69.7 (1C, C-5), 74.3 (1C, C-3), 75.3 (1C, C-1), 80.2 (1C, C-4), 126.1−129.7 (9C, Ar-C), 132.4, 134.7, 138.2 (3C, Ar-quat), 169.9, 170.0, 170.6 (3C, $-COCH_3$). HRMS (ESI) calcd for $C_{26}H_{29}NNaO_7$ $[M + Na]^+$: 490.1836; found: 490.1831.

*(2R,3S,4R,4aS,10bS)-5-Benzyl-3,4-dimethoxy-2-(methoxymethyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]isoquinoline **10**.* Compound **9** (104.5 mg, 0.21 mmol) was dissolved in dry CH_2Cl_2 (5 mL), under an inert atmosphere, then anhydrous iron trichloride (415 mg, 2.55 mmol) was added, and the reaction was stirred overnight at room temperature. Then, the mixture was diluted with CH_2Cl_2, washed with brine, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Finally, purification by flash column chromatography on silica gel (*n*-hexane/EtOAc, 30 → 50%) gave **10** as a pale yellow syrup (0.08 mmol, 38%). Data for **10**: R_f = 0.31 (30%, *n*-hexane/EtOAc). $[\alpha]_D^{20}$: +113.0 (c 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ 3.18 (1H, ddd, J = 2.2, 3.6, 9.9 Hz, H-5), 3.33 (1H, dd, J = 9.1, 9.8 Hz, H-4), 3.31 (1H, dd, J = 6.1, 9.6 Hz, H-2), 3.39 (1H, dd, J = 9.1, 9.6 Hz, H-3), 3.43 (3H, s, $-OCH_3$), 3.49 (3H, s, $-OCH_3$), 3.53−3.58 (2H, m, H-6), 3.67 (3H, s, $-OCH_3$), 3.79, 3.86 (2H, d, J = 16.3 Hz, PhCH_2N−), 3.95, 4.21 (2H, d, J = 13.9 Hz, PhCH_2N−), 5.21 (1H, d, J = 6.1 Hz, H-1), 7.01−7.48 (9H, m, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 49.2 (1C, PhCH_2N−), 59.2 (1C, $-OCH_3$), 59.5 (1C, $-OCH_3$), 60.2 (1C, C-2), 60.3 (1C, $-OCH_3$), 60.5 (1C, PhCH_2N−), 71.4 (1C, C-6), 71.8 (1C, C-5), 72.5 (1C, C-1), 80.0 (1C, C-3), 81.6 (1C, C-4), 125.9−128.5 (9C, Ar-C), 133.7, 135.8, 139.6 (3C, Ar-quat). HRMS (ESI) calcd for $C_{23}H_{29}NO_4$ $[M + Na]^+$: 406.1994; found: 406.1990.

*(2S,3R,3aS,9bR)-4-Benzyl-2-((R)-1,2-dimethoxyethyl)-3-methoxy-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]isoquinoline **4a**.* A mixture of compound **4** (160 mg, 0.33 mmol) and sodium methoxide (110 mg, 2.0 mmol) in dry methanol (10 mL/mmol) was stirred overnight at room temperature under an inert atmosphere. Then, the reaction mixture was diluted with methanol, filtered through Amberlite IR-120, and the solvent was removed under reduced pressure. The crude was dissolved in dry THF, NaH (60%, 6 equiv, 2.0 mmol) and MeI (30 equiv, 10.1 mmol) were added, and the reaction was stirred overnight. The mixture was diluted with CH_2Cl_2, neutralized with a saturated aqueous solution of NH_4Cl, and washed with water. The aqueous fraction was reextracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, concentrated under vacuum, and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 20%) affording compound **4a** (0.18 mmol, 54%) as a pale yellow viscous oil. Data **4a**: R_f = 0.17 (20%, *n*-hexane/EtOAc). $[\alpha]_D^{20}$: −13.0 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ 3.25, 3.73 (2H, d, J = 14.8 Hz, PhCH_2N−), 3.27 (1H, d, J = 5.4 Hz, H-2), 3.37 (3H, s, $-OCH_3$), 3.42, 4.20 (2H, d, J = 13.5 Hz, PhCH_2N−), 3.48 (6H, s, 2x $-OCH_3$), 3.51 (1H, dd, J = 5.6, 10.5 Hz, H-6a), 3.69−3.74 (1H, m, H-5), 3.79 (1H, dd, J = 2.0, 10.5 Hz, H-6b), 4.04 (1H, dd, J = 3.6, 9.2 Hz, H-4), 4.14 (1H, d, J = 3.5 Hz, H-3), 5.10 (1H, d, J = 5.5 Hz, H-1), 6.93−7.43 (9H, m, Ar-H). ^{13}C-NMR (126 MHz, $CDCl_3$); δ 53.0 (1C, PhCH_2N−), 57.6 (1C, $-OCH_3$), 58.3 (1C, $-OCH_3$), 59.3 (1C, $-OCH_3$), 59.9 (1C, PhCH_2N−), 67.9 (1C, C-2), 73.3 (1C, C-6), 75.2 (1C, C-1), 77.6 (1C, C-5), 78.4 (1C, C-4), 84.0 (1C, C-3), 125.8−129.1 (9C, Ar-C), 133.2, 134.8, 138.2 (3C, Ar-quat). HRMS (ESI) calcd for $C_{23}H_{29}NO_4$ $[M + Na]^+$: 406.1994; found: 406.1999.

*(1R)-1-((3R,3aR)-3-Acetoxy-2,3,3a,4,5,9b-hexahydrofuro-[3,2-c]isoquinolin-2-yl)-ethane-1,2-diyl diacetate **4b**.* A mixture of compound **4** (908 mg, 1.94 mmol) and Pd/C (10% mol, 61 mg, 0.3 equiv, 0.57 mmol) in EtOH (10 mL) was stirred under H_2 atmosphere at 50 °C for 4 h. The reaction mixture was filtered over Celite 521, and the solvent was removed under reduced pressure. Finally, purification by flash column chromatography on silica gel (*n*-hexane/EtOAc, 20−40%) gave **4b** (0.76 mmol, 54%) as a colorless syrup. Data for **4b**: R_f = 0.12 (40%, *n*-hexane/EtOAc). $[\alpha]_D^{20}$: +4.1 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ 1.99 (3H, s, $-COCH_3$), 2.00 (3H, s, $-COCH_3$), 2.10 (3H, s, $-COCH_3$), 3.50 (1H, d, J = 4.1 Hz, H-2), 3.92, 3.98 (2H, d, J = 15.2 Hz, PhCH_2N−), 4.14 (1H, dd, J = 5.8, 12.2 Hz, H-6a), 4.48 (1H, dd, J = 3.9, 9.4 Hz, H-4), 4.62 (1H, dd, J = 2.4, 12.2 Hz, H-6b), 4.98 (1H, d, J = 4.0 Hz, H-1), 5.31 (1H, d, J = 3.9 Hz, H-3), 5.35 (1H, ddd, J = 2.4, 5.8, 9.3 Hz, H-5), 7.10−7.43 (4H, m, Ar-H). ^{13}C NMR (151 MHz, MeOD); δ 20.5 (1C, $-COCH_3$), 20.7 (1C, $-COCH_3$), 20.8 (1C, $-COCH_3$), 47.6 (1C, PhCH_2N−), 63.7 (1C, C-2), 64.7 (1C, C-6), 69.9 (1C, C-5), 76.6 (1C, C-1), 78.0 (1C, C-4), 78.9 (1C, C-3), 126.9−131.5 (4C, Ar-C), 133.3, 137.0 (2C, Ar-quat), 171.2, 171.5, 172.4 (3C, $-COCH_3$). HRMS (ESI) calcd for $C_{19}H_{23}NO_7$ $[M + Na]^+$: 400.1372; found: 400.1371.

*(1R)-1-((3R,3aR)-3-Acetoxy-4-benzyl-5-oxo-2,3,3a,4,5,9b-hexahydrofuro[3,2c]isoquinolin-2-yl)ethane-1,2-diyl diacetate **4c**.* To a solution of compound **4** (84 mg, 0.18 mmol) in 1:1 THF/H_2O (5 mL:5 mL) was added $NaHCO_3$ (151 mg, 10 equiv, 1.80 mmol) and I_2 (343 mg, 7.5 equiv, 1.35 mmol). The mixture was stirred overnight at room temperature. Then, 10 mL of a saturated solution of $Na_2S_2O_3$ was added followed by the addition of 10 mL of a saturated solution of $NaHCO_3$ (10 mL). Then, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc, 30%) gave **4c** as a pale yellow syrup (70 mg, 0.15 mmol, 81%). Data for **4c**: R_f = 0.20 (30%, *n*-hexane/EtOAc). $[\alpha]_D^{20}$: +0.1 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ 1.87 (3H, s, $-COCH_3$), 1.91 (3H, s, $-COCH_3$), 2.00 (3H, s, $-COCH_3$), 3.90 (1H, dd, J = 4.3, 9.3 Hz, H-4), 4.01 (2H, m, H-2, H-6a), 4.40 (1H, dd, J = 2.2, 12.3 Hz, H-6b), 4.49, 5.28 (2H, d, J = 15.1 Hz, PhCH_2N−), 5.15 (1H, ddd, J = 2.2, 5.2, 9.3 Hz, H-5), 5.25 (1H, d, J = 11.1 Hz, H-1), 5.58 (1H, dd, J = 1.9, 4.2 Hz, H-3), 7.20−7.53 (8H, m, Ar-H), 8.20 (1H, d, J = 7.7 Hz, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 20.6 (1C, $-COCH_3$), 20.7 (1C, $-COCH_3$), 20.7 (1C,

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−COCH_3), 49.0 (1C, PhCH_2N−), 63.0 (1C, C-6), 64.9 (1C, C-2), 67.7 (1C, C-5), 73.2 (1C, C-1), 75.9 (1C, C-4), 76.4 (1C, C-3), 127.5−129.5 (9C, Ar-C), 132.8, 134.2, 136.9 (3C, Ar-quat), 162.5 (1C, *CO*), 169.6, 169.7, 170.5 (3C, −*CO*CH_3). HRMS (ESI) calcd for $C_{26}H_{29}NO_8$ $[M + Na]^+$: 504.1634; found: 504.1641. Anal. calcd for $C_{26}H_{27}NO_8$: C, 64.86; H, 5.65; N, 2.91; found C, 64.94; H, 5.90; N, 2.79.

(2S,3R,3aS,9bR)-4-Benzyl-3-(benzyloxy)-2-(1,2-bis-(benzyloxy)ethyl)-2,3,3a,9-b-tetrahydrofuro[3,c]isoquinolin-5(4H)-one ***4d***. A mixture of compound **4c** (54 mg, 0.11 mmol) and sodium methoxide (18 mg, 0.34 mmol) in dry methanol (3 mL) was stirred overnight at room temperature. Then, the reaction mixture was diluted with methanol, filtered through Amberlite IR-120, and the solvent was removed under reduced pressure. The residue was dissolved in anhydrous DMF, and NaH (60%, 34 mg, 7.5 equiv, 0.84 mmol) was added at 0 °C under an inert atmosphere. The mixture was stirred for 15 min, and then BnBr (0.1 mL, 5.0 equiv, 0.56 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with some drops of MeOH, diluted with CH_2Cl_2, and washed with a saturated solution of NH_4Cl and H_2O. The organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash column chromatography on silica gel (*n*-hexane/EtOAc, 5% to 20%) gave compound **4d** (63 mg, 0.10 mmol, 86%), as a pale yellow viscous oil. Data for **4d**: R_f = 0.22 (20%, *n*-hexane/EtOAc). $[\alpha]_D^{20}$: +2.9 (c 0.1, $CHCl_3$).^{1}H NMR (500 MHz, $CDCl_3$); δ 3.62 (1H, dd, J = 4.9, 10.6 Hz, H-6a), 3.85 (1H, J = 1.6, 10.9 Hz, H-6b), 4.01 (2H, m, H-4, H-5), 4.08 (1H, dd, J = 1.9, 5.9 Hz, H-2), 4.22 (1H, d, J = 11.5 Hz, PhCH_2N−), 4.29, 5.39 (2H, d, J = 15.3 Hz, PhCH_2N−), 4.43 (5H, m, 2x PhCH_2N−, H-3), 4.76 (1H, d, J = 11.7 Hz, PhCH_2N−), 5.20 (1H, d, J = 5.9 Hz, H-1), 7.14−7.49 (23H, m, Ar-H), 8.24 (1H, dd, J = 1.4, 7.8 Hz, Ar-H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 48.1 (1C, PhCH_2N−), 63.5 (1C, C-2), 71.0 (1C, C-6), 72.0 (1C, PhCH_2N−), 72.9 (1C, C-1), 73.0 (1C, PhCH_2N−), 73.4 (1C, PhCH_2N−), 76.3 (1C, C-5), 78.6 (1C, C-3), 83.1 (1C, C-4), 127.3−129.2 (24C, Ar-C), 132.5, 134.9, 136.8, 137.6, 138.4, 138.8 (6C, Ar-quat), 163.2 (1C, *CO*). HRMS (ESI) calcd for $C_{41}H_{39}NO_5$ $[M + Na]^+$: 648.2726; found: 648.2730.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04804.

Mono- and bidimensional NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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